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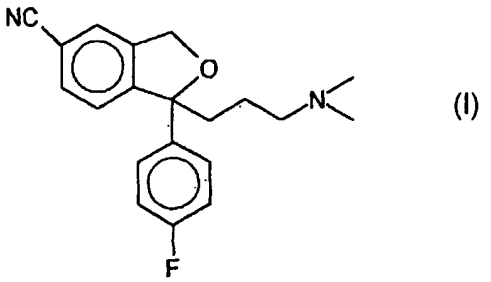
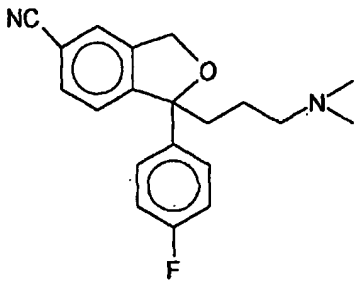
(54) Title: PROCESS FOR THE PREPARATION OF HIGH PURITY CITALOPRAM AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS



(I)



I(A)

(57) Abstract: This invention discloses an improved process for the preparation of high purity citalopram base and its hydrobromide salt of formulae (I) and (Ia): which comprises: i. Isolation of crude citalopram base after water work up of the reaction into a non polar aromatic or dialkyl ether solvent. ii. Extraction of the citalopram base into aqueous organic acid. iii. Neutralization of acid layer with organic base to a controlled pH (7.0-8.0) iv. Extraction of the pure base into a non-polar aromatic or dialkyl ether solvent and crytallization form the same solvent after concentrating to certain volume under reduced pressure. v. Preparation of high purity citalopram hydrobromide in a non-polar aromatic or dialkyl ether solvent using 40-50 % HBr in acetic acid as HBr source and crystallizing out form the same solvent. Alternatively preparation of HBr salt in aqueous medium using aqueous HBr and crystallizing out from the same medium at 0 10 °C. vi. Recrystallization of high purity citalopram hydrobromide salt of pharmaceutically acceptable grade form a mixture of alcoholic solvent.

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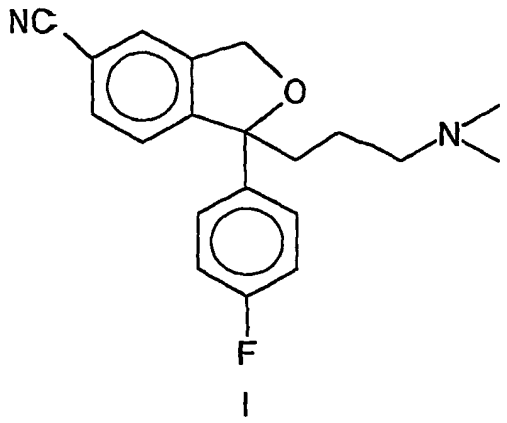
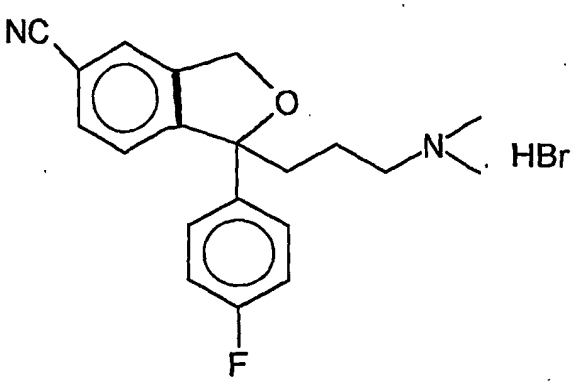
PROCESS FOR THE PREPARATION OF HIGH PURITY CITALOPRAM AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

The present invention relates to an improved process for the preparation of high purity citalopram and its pharmaceutically acceptable salts. The particular salt envisaged by the invention is the hydrobromide salt. Citalopram having the Formula-I and its hydrobromide addition salt of the Formula-I(a) given below are well-known antidepressant drug available in the market. It is a selective, centrally active serotonin (5-hydroxy trypamine, 5-HT) re-uptake inhibitor, accordingly having antidepressant activities.



I

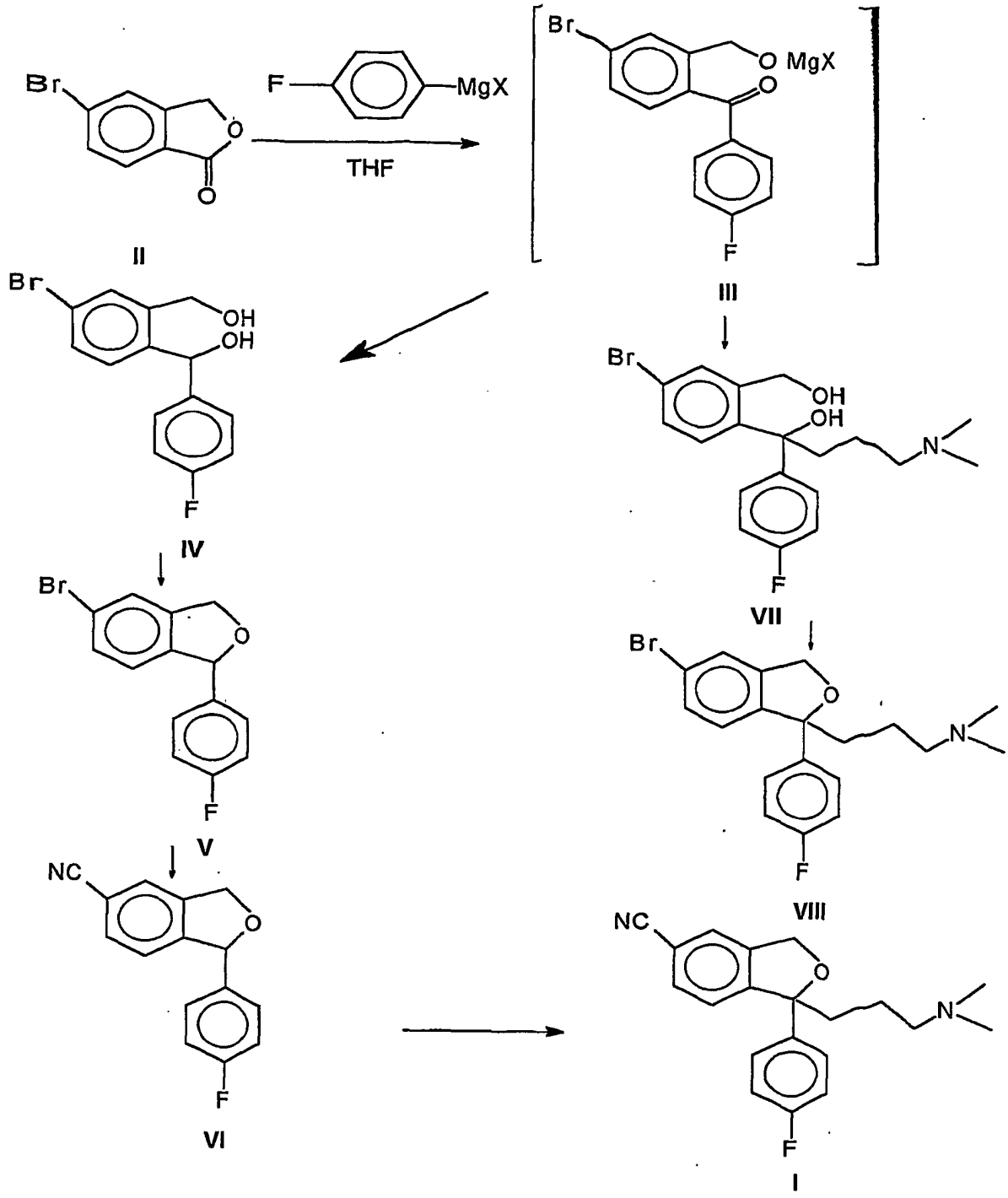


I(a)

BACKGROUND OF THE INVENTION:

The antidepressant activity of citalopram has been reported in several publications, eg. H. Dufour, et al, **Int. Clin. Psychopharmacol.** 2, 225 (1987), L. Timmerman, et al, ibid, 239, and A. Gravem, **Acta Psychiatr. Scand.**, 75, 478 (1987).

Citalopram was first disclosed in DE Patent no. 2,657,271 corresponding to US Patent no. 4,136,193. This patent describes the process for the preparation of citalopram by two methods as shown in Scheme-I.



SCHEME–I

In the first route shown in Scheme I, 5-bromophthalide of the Formula-II was reacted with p-fluorophenylmagnesium halide to get a benzophenone derivative of the Formula-III. At this stage, this benzophenone derivative can be either reduced with lithium aluminium hydride or alkylated with 3-dimethylaminopropylmagnesium halide.

Accordingly, in the first route, the lithium aluminium hydride reduced product of the Formula-IV was cyclized with 60% phosphoric acid to get the benzofuran derivative of the Formula-V. This bromobenzofuran derivative is reacted with copper cyanide to get the corresponding cyano derivative of the Formula-VI. The cyano derivative was alkylated with 3-dimethylaminopropyl chloride to get the citalopram of the Formula-I.

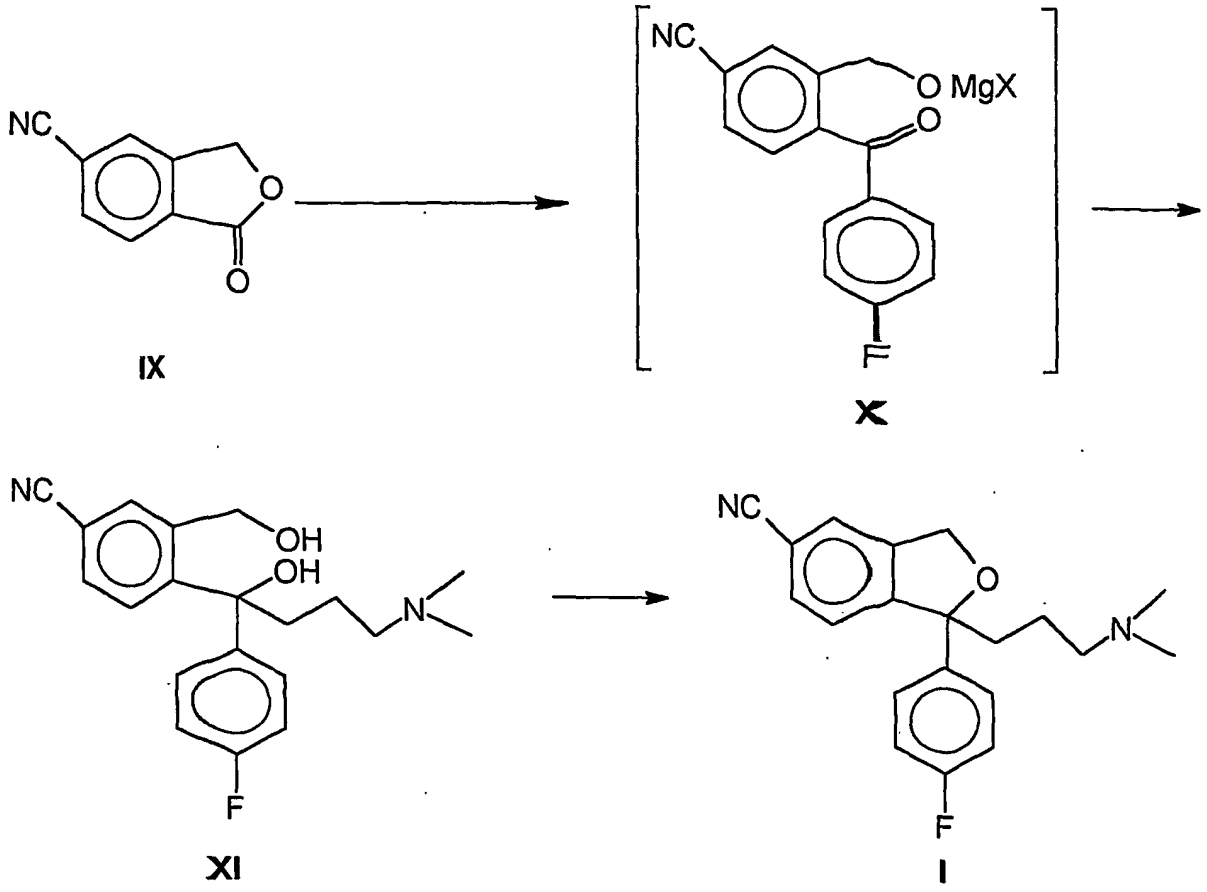
In the second route, also shown in Scheme 1, benzophenone derivative of the Formula-III was reacted with 3-dimethylaminopropylmagnesium halide to get the dihydroxy compound of the Formula-VII. This dihydroxy compound was cyclized with 60% phosphoric acid to get the bromo analogue of the Formula-VIII of citalopram. The bromo group was displaced by cyano group using copper cyanide to get the citalopram of the Formula-I.

The citalopram obtained from both the routes was purified by dissolving in ether and extracting into 25% aqueous acetic acid. The acetic acid solution was made alkaline with 10N aqueous sodium hydroxide solution and extracted with ether. Purity of this purified citalopram was not mentioned in the patent. In the same patent it was mentioned that the hydrobromide salt of citalopram was prepared by conventional method. The melting point (182 - 183°C) of the hydrobromide salt of citalopram reported in this patent is 4 - 5°C lower than the one reported in EP Patent no. 171,193. Purity of the pharmaceutically acceptable hydrobromide salt of citalopram was also not mentioned in the patent.

The new route shown in Scheme-II, for the preparation of citalopram described in EP Patent no.171,193 starts with 5-cyanophthalide of the Formula-IX and follows the double Grignard path of original patent process. 5-Cyanophthalide was reacted with p-fluorophenylmagnesium halide to get the benzophenone derivative of the Formula-X which was reacted *in situ* with 3-dimethylaminopropylmagnesium halide to get the dihydroxy derivative of the Formula-XI. This dihydroxy compound was cyclized with 70% sulfuric acid to get the citalopram of the Formula-I.

The citalopram prepared by this method is extracted into toluene at pH 10.0 and the extracted product was twice passed through a bed of silicagel (weight equal to product). After treatment with charcoal, hydrogen bromide gas is introduced into the acetone - toluene solution of citalopram base and made acidic until pH 3.0. pH is raised to 7.0 by adding some of the above citalopram base containing solution. The crude citalopram hydrobromide thus obtained was recrystallized from water after charcoal treatment. The crystals from the first recrystallization were dissolved in methanol - isopropyl alcohol medium and recrystallized after charcoal treatment. The material from this 2nd

recrystallization is dissolved in a mixture of methanol and acetone and filtered with charcoal and recrystallized to get the pure citalopram hydrobromide with a melting point



SCHEME-II

of 185 - 186°C. After three recrystallization a loss of 23 - 26% was reported in this process. Also, the chemical purity of the final crystallization material is not mentioned.

Six solvents (a total of 46 - 47 liters per kg of citalopram hydrobromide) were used involving three recrystallizations and it took more than four days time.

In the above said process, controlling the molar quantity of HBr gas seems to be difficult. So readjusting of pH with spare citalopram base solution is not an appropriate method for commercial scale operations. Also, filtering citalopram base through silica gel column and three recrystallization techniques for purification of the hydrobromide salt with six solvents over a period of 4 - 5 days is not an economically viable process for plant scale

operations. As a mixture of solvents were used in recrystallization technique, their reuse is again a tedious and difficult process.

In the international patent no. WO 00/23431, citalopram base was dissolved in 15 times acetone and converted to its hydrobromide salt using aqueous HBr solution and isolated the salt by cooling and filtration. Purity of the citalopram hydrobromide is found to be ≥90% (by HPLC). This raw citalopram hydrobromide is recrystallized from water. However, no yield and quality of the product is mentioned in this patent.

In summary, the original patent for pharmaceutically acceptable hydrobromide salt of citalopram does not describe any process for making it. Also, the quality of the product is not mentioned.

The improved process for citalopram and its hydrobromide salt described in EP Patent no. 171,943 is not suitable for commercial scale as mentioned above.

In the international Patent no. 00/23431 yield and quality of the citalopram hydrobromide is not mentioned after recrystallization from water.

Citalopram has become a well-known antidepressant drug that has now been in the market and shown great promise as a valuable antidepressant drug with few side effects. To meet the market demand a simple and convenient process for preparing citalopram hydrbromide on a commercial scale is very much needed.

Keeping in view of the difficulties in commercialization of the processes disclosed in the above mentioned patents, we aimed our research work to develop a simple and convenient process for the preparation of citalopram and its hydrobromide salt which can be utilised for their commercial scale production with very high purity (99.5%).

Accordingly, the main objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salts, particularly, hydrobromide salt of high purity (>99.5%).

According to another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) which is not only simple but also useful for their commercial production.

According to still another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) by using weak aqueous organic acid such as acetic acid, propionic acid, succinic acid, oxalic acid to extract the crude citalopram base into water medium from the impurities.

According to yet another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) by neutralizing the weak organic salts with weak bases such as aqueous ammonia, monomethyl amine, dimethyl amine or triethyl amine to a controlled pH.

According to still another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) by extracting the purified base into a non-polar ether solvent or an aromatic solvent.

According to yet another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) by isolating the crystalline citalopram from the same non-polar ether solvent or aromatic solvent by keeping the concentration at a certain level.

According to another objective of the present invention is to provide an improved process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt, of high purity (>99.5%) by employing aqueous HBr or HBr as commercially available HBr in acetic acid in the case of organic solvent as the medium of reaction.

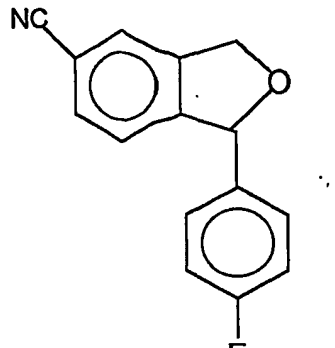
During our sustained research to develop a simple process for the preparation of citalopram and its pharmaceutically acceptable salt, particularly hydrobromide salt which can be used for their commercial production, we observed that a promising approach for such process would be to:

(a) replacing hazardous lithium aluminium hydride with sodium borohydride for the preparation of dihydroxy compound of formula IV shown in scheme 1 is very much cost effective
(b) avoidance of high vacuum distillation at the stage of formation of crude intermediate of the formula V shown in scheme 1 is very much advantageous
(c) removing the impurities from the intermediate of the formula VI instead of from the compound of the formula V shown in scheme 1 employing simple crystallization technique, thereby making the purification process simpler and more effective
(d) improve the quality of citalopram base formed in the reaction to an appropriate level so that the quality of hydrobromide salt would be of pharmaceutical grade
(e) select proper solvent system and conditions to keep the impurities present in citalopram base in solution form while making the salt

(f) select proper source of hydrogen bromide other than HBr gas to make the salt and

(g) avoid recrystallization technique, if possible to minimize the losses of citalopram salt, especially hydrobromide salt.

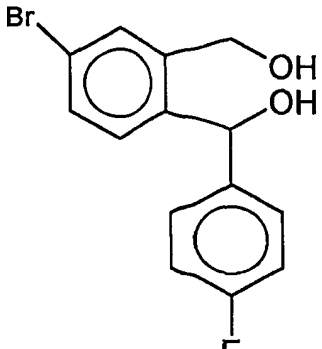
In our co-pending Indian application no 157 MAS 01 we have described an improved process for the preparation of 5-cyanophthalane of the formula VI.



VI

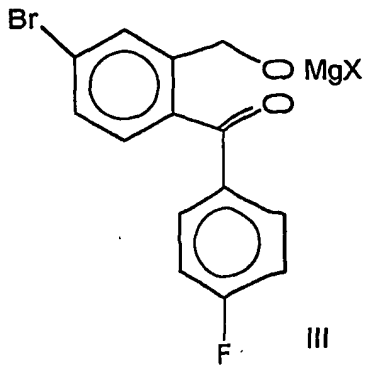
which comprises:

(i) preparing the compound of the formula IV



IV

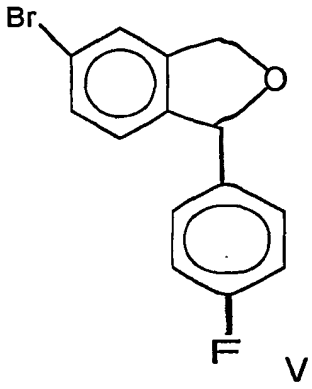
by reducing an unisolaable magnesium salt of benzophenone derivative of the formula III.



III

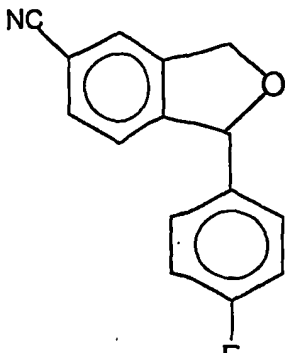
using sodium borohydride in the presence of a protic solvent

(ii) reacting the compound of the formula IV obtained in step(i) with an acid catalyst in a non-polar solvent to obtain a compound of the formula V.



V

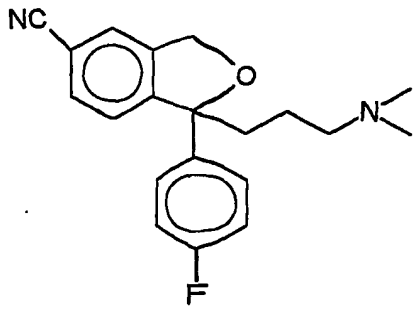
(iii) reacting the compound of the formula V obtained in step (ii) with copper (I) cyanide in a polar solvent medium and isolating the resulting cyano compound, by recrystallization by using polar and /or alcoholic solvents to obtain the compound of formula VI.



VI

The present invention has been developed based on our above mentioned observations and in continuation of the process disclosed in our above mentioned co-pending application.

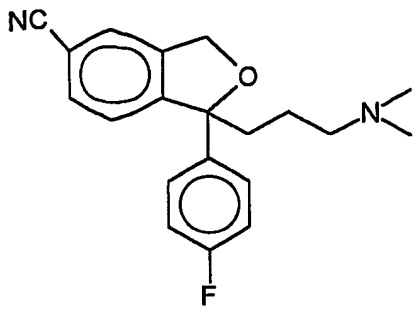
Accordingly, the compound of formula VI was reacted with strong base such as NaH in DMSO medium and quenched with 3-dimethylaminopropylchloride to get the crude citalopram base of formula I.



I

Accordingly, we found that if, one extracts the crude citalopram base into aqueous organic acids and controls the pH of this aqueous medium while extracting the base back into organic solvents, a lot of impurities can be eliminated at this stage itself. Also by extracting the base into a reasonably less polar solvent, the quality of citalopram base can be improved. Further, if the source of HBr is non-gaseous, it would be easy to control the quantity required in making the citalopram hydrobromide. In addition, we have found that hydrobromide salt can be exclusively formed in the presence of a weak organic acid like acetic acid.

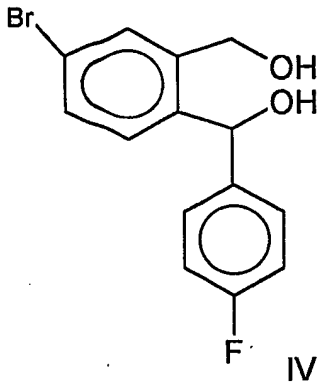
Accordingly, the present invention provides an improved process for the preparation of citalopram of the formula I and its pharmaceutically acceptable salts,



I

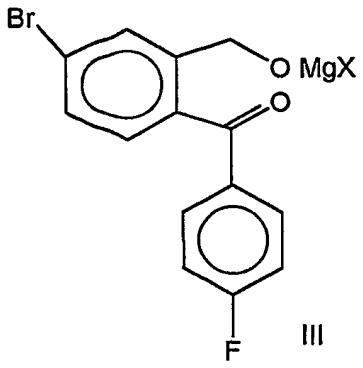
which comprises:

(i) preparing the compound of the formula IV



IV

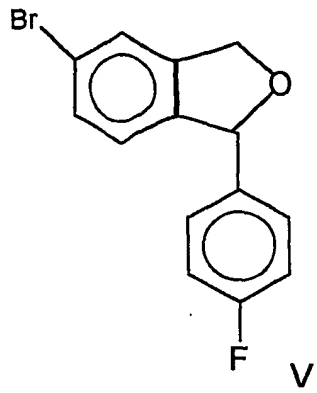
by reducing an unisolable magnesium salt of a benzophenone derivative of the formula III.



III

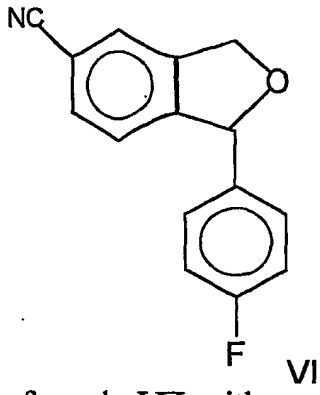
using sodium borohydride in the presence of a protic solvent

(ii) reacting the compound of the formula IV obtained in step(i) with an acid catalyst in a non-polar solvent to obtain a compound of the formula V



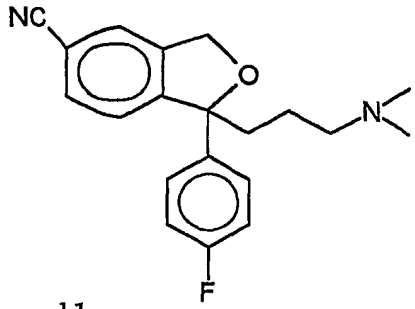
V

(iii) reacting the compound of the formula V obtained in step (ii) with copper (I) cyanide in a polar solvent medium and isolating the resulting cyano compound of the formula VI, by recrystallization by using polar and /or alcoholic solvents.



VI

(iv) reacting the compound of the formula VI with a strong base in DMSO medium followed by quenching with the required side chain to get the crude citalopram base of the formula I in the reaction mass.



I

(v) pouring the reaction mass containing citalopram obtained in steep (iv) above into water and extracting the citalopram from an organic solvent.

(vi) extracting the citalopram from the organic solvent using dilute aqueous organic acid.

(vii) adjusting the pH of the resulting aqueous organic acid layer to 7.0 to 8.0 using a weak organic base.

(viii) extracting the liberated citalopram using a non-polar ether or aromatic solvent.

(ix) crystallizing the citalopram from the same solvent after concentrating and isolating by filtration and if desired.

(x) forming the pharmaceutically acceptable salt of the citalopram by conventional methods.

The protic solvent used in step (i) may be methanol, ethanol, or isopropanol preferably methanol. The acid catalyst used in step (ii) may be sulfuric acid, p-toluene sulfonic acid, or benzene sulfonic acid, preferably p-toluene sulfonic acid. The polar solvent medium used in copper (I) cyanide reaction of step (iii) may be pyridine, dimethyl formamide, or dimethylacetamide, preferably dimethyl formamide. The solvents used for crystallization of compound of formula VI in step (iii) may be methanol, ethanol or isopropyl alcohol with or without diemthyl formamide or dimethyl acetamide, preferably isopropyl alcohol with or without dimethyl formamide.

The strong base used in step (iv) may be sodium hydride or potassium t-butoxide, preferably sodium hydride.

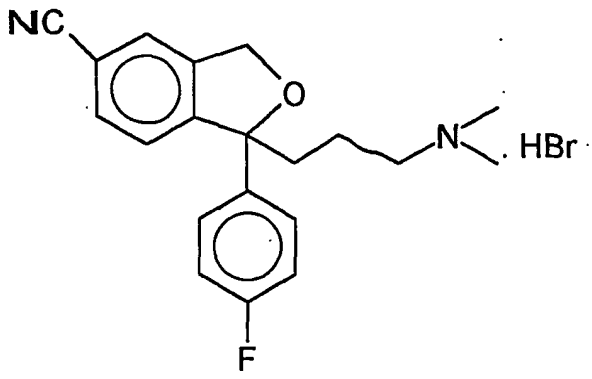
The aromatic solvent used in the step (v) may be selected from benzene, toluene, xylene etc. preferably into toluene. The organic acid used in step (vi) may be selected from acetic acid, propionic acid, succinic acid, oxalic acid preferably acetic acid. The organic base used in step (vii) may be selected from ammonia, monomethyl amine, dimethyl amine, triethyl amine preferably ammonia.

The non-polar solvent used in step (viii) may be selected from diethyl ether, isoporpyl ether, t-butyl methyl ether and the aromatic solvent may be selected from, toluene, benzene, etc., preferably isopropyl ether or toluene.

The volume of solvent used in step (ix) for crystallization of the citalopram base may be in the range of 2-4 to its weight preferably 2- 3 and the temperature at which the base can be isolated is in the range of 10 to 25°C, preferably 20 – 25°C.

The citalopram base thus obtained is found to be of high purity (>99.5%).

According to another embodiment of the present invention there is also provided an improved process for the preparation of high purity (99.8%) citalopram hydrobromide salt of formula I(a)



I(a)

which comprises:

a. dissolution of high purity (99.5%) citalopram obtained as described above in a non- polar aromatic or dialkyl ether solvent and addition of molar quantity of 40 – 50% HBr in acetic acid.
b. isolating the citalopram hydrobromide by filtration from the organic solvent of step (a) at a temperature in the range of 0 – 25° C.
c. if desired , recrystallizing the formed citalopram hydrobromide from a mixture of alcoholic solvents.

The solvent used in step (a) may be isopropyl ether, ethyl acetate, t-butyl methyl ether, toluene, IPA etc. preferably ethyl acetate or isopropyl ether.

The solvent used for recrystallization of citalopram hydrobromide in step (c) may be metahnol, ethanol, IPA preferably methanol and IPA.

The temperature employed in step (b) may be preferably in the range of 5 to 10°C.

Citalopram hydrobromide prepared by this method was found to be of >99.8% purity.

(or)

a. suspension of the high purity (>99.5%) citalopram obtained above in water and addition of molar quantity of commercially available aqueous hydrobromic acid.
b. decolorization of the resulting solution with charcoal and crystallization of the citalopram hydrobromide.
c. Isolation of citalopram hydrobromide by filtration.

The crystallization temperature mentioned in step (a) may be 0-25°C preferably in the range of 15-25°C. The isolation temperature mentioned in step (b) may be in the range of 0-25°C preferably in the range of 5-10°C.

The details of the invention are described in the Examples given below which are provided to illustrate the invention only and therefore should not be construed to limit the scope of the present invention.

Example – 1.

Preparation of citalopram.

(a) Preparation of 4–bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol of formula-IV.

The Grignard solution prepared from 90gr of 4-fluorobromobenzene and 13gr magnesium turnings in 450ml of THF was added drop wise to a suspension of 5-bromophthalide (100gr) in THF (600ml) at –10 to -5°C under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at same temperature for another 3hrs and treated with a slurry of sodium borohydride (25gr) in 300ml of ethyl alcohol keeping the temperature below 10°C. After maintaining for 1hr at 10°C, the reaction mixture was quenched into dil. hydrochloric acid (220ml conc HCl in 1750ml water). After stirring the reaction mass for 30min, the layers were separated. The aqueous layer was extracted with 3 x 100ml of toluene. Combined organic layer was washed with saturated sodium chloride (300ml) and dried over sodium sulfate. Solvents were removed under vacuum below 60°C to get the crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr). This compound is suitable for use in next stage of the process.

(b) Preparation of 1-(4-fluorophenyl)-5-bromophthalan of formula-V.

The crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr) obtained from step (a) above was dissolved in 1000ml of toluene. To this solution was added 10gr of p-toluene sulfonic acid and heated to reflux. Water formed in the reaction was removed using Dean-stark apparatus. When the water formation was over, reaction mass was cooled to room temperature and 1000ml of water added. After stirring for 30min organic layer was separated and the aqueous layer extracted with 3 x 100ml of toluene. The combined organic layer was washed with 2 x 250ml of 5% sodium carbonate solution. Finally the organic layer was washed with saturated sodium chloride. Toluene was removed under vacuum below 60°C to get the crude **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) as an oil.

(c) Preparation of 1-(4-fluorophenyl)-5-cyanophthalan of formula VI.

To a solution of the **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) obtained in step (b) above in DMF (360) was added freshly prepared copper (I) cyanide (76gr). The resulting suspension was slowly heated to reflux temperature and maintained at reflux for 4 – 5hrs. After cooling the reaction mass to a temperature in the range of 40 – 50°C, aqueous ammonia (200ml, 10% w/v) was added and stirred for 30min. After filtering off the insoluble salts, layers were separated. The organic layer was washed with 200ml of dil. ammonia (10% solution). Combined aq. layers were extracted with 100ml of toluene. Toluene layers were combined and the solvent distilled off under vacuum at 50 – 60°C to give the crude **1-(4-fluorophenyl)-5-cyanophthalan** of the formula VI (120gr) as a semisolid. The crude compound was dissolved in 500ml of IPA by heating to 60 – 70°C and treated with 5gr of charcoal. After filtration, cooling to a temperature in the range of 20 – 25°C, it was kept at this temperature for 8 – 12hrs. Filtration of the solids and washing with 100ml of IPA gave light yellow crystalline solid **1-(4-fluorophenyl)-5-cyanophthalan** of the formula V (100gr), m.p. 96 – 97°C. Purity by HPLC is 98%.

(d) Preparation of 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan of formula I.

A solution of dimsyl sodium in DMSO was prepared by adding 22gr of 50% sodium hydride in parafin oil to DMSO (1000ml) at 20 – 25°C and slowly heating to 60 – 65°C under nitrogen. To this solution kept at a temperature in the range of 20 – 25°C, was added a solution of 1-(4-fluorophenyl)-5-cyanophthalan of the formula V obtained in step (c) above (100gr) in DMSO (200ml) slowly in 2 – 3hrs. After maintaining for 15 –

20min, a solution of 3-dimethylaminopropylchloride (56gr) in toluene (120ml) was slowly added keeping the temperature between 25 – 30°C. After the addition is over, reaction mixture was maintained at this temperature for 30min and decomposed by adding 50ml of methanol. The reaction mixture was poured into 3000ml of water and extracted with 1000ml of toluene. Aqueous layer was again extracted with 500ml of toluene. The combined toluene layer containing crude citalopram base [**1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan] of formula I** can be directly taken for purification as per one of the below examples.

(e) Purification of crude citalopram base using acetic acid as organic acid and ammonia as organic base.

The combined organic layer obtained in step (d) above was extracted with 2 x 1000ml of 20% aqueous acetic acid. The combined aqueous acetic acid layer was neutralized with aqueous ammonia (25%) to get the pH of 7 – 7.5. After the pH adjustment, 500ml of isopropyl ether was added and stirred for 15min. Isopropyl ether layer was separated and the aqueous layer extracted with 2 x 300ml of isopropyl ether. The combined isopropyl ether layer was treated with carbon (10gr) and filtered. The filtrate was distilled off under vacuum below 45°C to leave about 200ml of isopropyl ether. The reaction mixture was cooled to room temperature under stirring and filtered to get white crystalline solid citalopram base of the formula I (100gr). M.p. 95°C, purity by HPLC 99. 5%.

Example – 2.

Preparation of citalopram.

(a) Preparation of 4-bromo-(2-hydroxymethyl)- phenyl-(4^1-fluorophenyl)methanol of formula-IV.

The Grignard solution prepared from 90gr of 4-fluorobromobenzene and 13gr magnesium turnings in 450ml of THF was added drop wise to a suspension of 5-bromophthalide (100gr) in THF (600ml) at –10 to –5°C under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at same temperature for another 3hrs and treated with a slurry of sodium borohydride (25gr) in 300ml of isopropyl alcohol keeping the temperature below 10°C. After maintaining for 1hr at 10°C, the reaction mixture was quenched into dil. hydrochloric acid (220ml conc HCl in 1750ml water). After stirring the reaction mass for 30min, the layers were separated. The aqueous layer was extracted with 3 x 100ml of toluene. Combined organic layer was washed with saturated sodium chloride (300ml) and dried over sodium sulfate. Solvents were removed under vacuum below 60°C to get the crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr). This compound is suitable for use in next stage of the process.

(b) Preparation of 1-(4-fluorophenyl)-5-bromophthalan of formula-V.

The crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr) obtained from step (a) above was dissolved in 1000ml of toluene. To this solution was added 10gr of sulfuric acid and heated to reflux. Water formed in the reaction was removed using Dean-stark apparatus. When the water formation was over, reaction mass was cooled to room temperature and 1000ml of water added. After stirring for 30min organic layer was separated and the aqueous layer extracted with 3 x 100ml of toluene. The combined organic layer was washed with 2 x 250ml of 5% sodium carbonate solution. Finally the organic layer was washed with saturated sodium chloride. Toluene was removed under vacuum below 60°C to get the crude **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) as an oil.

(c) Preparation of 1-(4-fluorophenyl)-5-cyanophthalan of formula VI.

To a solution of the **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) obtained in step (b) above in dimethyl acetamide (360) was added freshly prepared copper (I) cyanide (76gr). The resulting suspension was slowly heated to 150 – 155°C and maintained at that temperature for 4 – 5hrs. After cooling the reaction mass to a temperature in the range of 40 – 50°C, aqueous ammonia (200ml, 10% w/v) was added and stirred for 30min. After filtering off the insoluble salts, layers were separated. The organic layer was washed with 200ml of dil. ammonia (10% solution). Combined aq. layers were extracted with 100ml of toluene. Toluene layers were combined and the solvent distilled off under vacuum at 50 — 60°C to give the crude **1-(4-fluorophenyl)-5-cyanophthalan** of the formula VI (120gr) as a semisolid. The crude compound was dissolved in 500ml of IPA by heating to 60 – 70°C and treated with 5gr of charcoal. After filtration, cooling to a temperature in the range of 20 – 25°C, it was kept at this temperature for 8 – 12hrs. Filtration of the solids and washing with 100ml of IPA gave light yellow crystalline solid **1-(4-fluorophenyl)-5-cyanophthalan** of the formula V (100gr), m.p. 96 – 97°C. Purity by HPLC is 98%.

(d) Preparation of 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan of formula I.

A solution of dimsyl sodium in DMSO was prepared by adding 22gr of 50% sodium hydride in paraffin oil to DMSO (1000ml) at 20 – 25°C and slowly heating to 60 – 65°C under nitrogen. To this solution kept at a temperature in the range of 20 – 25°C, was added a solution of 1-(4-fluorophenyl)-5-cyanophthalan of the formula V obtained in step (c) above (100gr) in DMSO (200ml) slowly in 2 – 3hrs. After maintaining for 15 — 20min, a solution of 3-dimethylaminopropylchloride (56gr) in toluene (120ml) was slowly added keeping the temperature between 25 – 30°C. After the addition is over, reaction mixture was maintained at this temperature for 30min and decomposed by adding 50ml of methanol. The reaction mixture was poured into 3000ml of water and

extracted with 1000ml of toluene. Aqueous layer was again extracted with 500ml of toluene. The combined toluene layer containing crude citalopram base [**1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan] of formula I** can be directly taken for purification as per one of the below examples.

(e) Purification of citalopram base using oxalic acid as acid and triethyl amine as base.

The combined organic layer from example 2 was extracted with 2 x 1000ml of 10% oxalic acid. The combined aqueous oxalic acid layer was neutralized with aqueous triethyl amine (25%) to get the pH of 7 – 7.5. After the pH adjustment, 500ml of isopropyl ether was added and stirred for 15min. Isopropyl ether layer was separated and the aqueous layer extracted with 2 x 300ml of isopropyl ether. The combined isopropyl ether layer was treated with carbon (10gr) and filtered. The filtrate was distilled off under vacuum below 45°C to leave about 200ml of isopropyl ether. The reaction mixture was cooled to room temperature under stirring and filtered to get white crystalline solid citalopram base of the formula I (95gr). M.p. 95°C, purity by HPLC 99.5%.

Example – 3.

Preparation of citalopram.

(a) Preparation of 4-bromo-(2-hydroxymethyl)–phenyl-(4^1-fluorophenyl)methanol of formula-IV.

The Grignard solution prepared from 90gr of 4-fluorobromobenzene and 13gr magnesium turnings in 450ml of THF was added drop wise to a suspension of 5-bromophthalide (100gr) in THF (600ml) at –10 to -5°C under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at same temperature for another 3hrs and treated with a slurry of sodium borohydride (25gr) in 300ml of methanol keeping the temperature below 10°C. After maintaining for 1hr at 10°C, the reaction mixture was quenched into dil. hydrochloric acid (220ml conc HCl in 1750ml water). After stirring the reaction mass for 30min, the layers were separated. The aqueous layer was extracted with 3 x 100ml of toluene. Combined organic layer was washed with saturated sodium chloride (300ml) and dried over sodium sulfate. Solvents were removed under vacuum below 60°C to get the crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr). This compound is suitable for use in next stage of the process.

(b) Preparation of 1-(4–fluorophenyl)-5-bromophthalan of formula-V.

The crude oily **4-bromo-(2-hydroxymethyl)-phenyl-(4^1-fluorophenyl)methanol** of the formula IV (200gr) obtained from step (a) above was dissolved in 1000ml of toluene. To this solution was added 10gr of benzene sulfonic acid and heated to reflux. Water formed in the reaction was removed using Dean-stark apparatus. When the water formation was over, reaction mass was cooled to room temperature and 1000ml of water added. After stirring for 30min organic layer was separated and the aqueous layer extracted with 3 x 100ml of toluene. The combined organic layer was washed with 2 x 250ml of 5% sodium carbonate solution. Finally the organic layer was washed with saturated sodium chloride. Toluene was removed under vacuum below 60°C to get the crude **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) as an oil.

(c) Preparation of 1-(4-fluorophenyl)-5-cyanophthalan of formula VI.

To a solution of the **1-(4-fluorophenyl)-5-bromophthalan** of the formula V (150gr) obtained in step (b) above in pyridine (360) was added freshly prepared copper (I) cyanide (76gr). The resulting suspension was slowly heated to reflux temperature and maintained at reflux for 4 – 5hrs. After cooling the reaction mass to a temperature in the range of 40 – 50°C, aqueous ammonia (200ml, 10% w/v) was added and stirred for 30min. After filtering off the insoluble salts, layers were separated. The organic layer was washed with 200ml of dil. ammonia (10% solution). Combined aq. layers were extracted with 100ml of toluene. Toluene layers were combined and the solvent distilled off under vacuum at 50 — 60°C to give the crude **1-(4-fluorophenyl)-5-cyanophthalan** of the formula VI (120gr) as a semisolid. The crude compound was dissolved in 500ml of IPA by heating to 60 – 70°C and treated with 5gr of charcoal. After filtration, cooling to a temperature in the range of 20 – 25°C, it was kept at this temperature for 8 – 12hrs. Filtration of the solids and washing with 100ml of IPA gave light yellow crystalline solid **1-(4-fluorophenyl)-5-cyanophthalan** of the formula V (100gr), m.p. 96 – 97°C. Purity by HPLC is 98%.

(d) Preparation of 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan of formula I.

A solution of dimsyl sodium in DMSO was prepared by adding 22gr of 50% sodium hydride in parafin oil to DMSO (1000ml) at 20 – 25°C and slowly heating to 60 – 65°C under nitrogen. To this solution kept at a temperature in the range of 20 – 25°C, was added a solution of 1-(4-fluorophenyl)-5-cyanophthalan of the formula V obtained in step (c) above (100gr) in DMSO (200ml) slowly in 2 – 3hrs. After maintaining for 15 — 20min, a solution of 3-dimethylaminopropylchloride (56gr) in toluene (120ml) was slowly added keeping the temperature between 25 – 30°C. After the addition is over, reaction mixture was maintained at this temperature for 30min and decomposed by adding 50ml of methanol. The reaction mixture was poured into 3000ml of water and extracted with 1000ml of toluene. Aqueous layer was again extracted with 500ml of

toluene. The combined toluene layer containing crude citalopram base [1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-cyanophthalan] of formula I can be directly taken for purification as per one of the below examples.

(e) Purification of crude citalopram base using acetic acid as organic acid and triethylamine as base.

The combined organic layer obtained in step (d) above was extracted with 2 x 1000ml of 20% aqueous acetic acid. The combined aqueous acetic acid layer was neutralized with triethylamine to get the pH of 8.0 – 8.5. After the pH adjustment, 500ml of isopropyl ether was added and stirred for 15min. Isopropyl ether layer was separated and the aqueous layer extracted with 2 x 300ml of isopropyl ether. The combined isopropyl ether layer was treated with carbon (10gr) and filtered. The filtrate was distilled off under vacuum below 45°C to leave about 200ml of isopropyl ether. The reaction mixture was cooled to room temperature under stirring and filtered to get white crystalline solid citalopram base of the formula I (100gr). M.p. 95°C, purity by HPLC 99.5%.

Example 4

Preparation of citalopram hydrobromide.

(a) Using isopropyl ether as solvent and HBr in acetic acid as HBr source.

To a stirred suspension of pure citalopram base (100gr) in 300ml of isopropyl ether was added a solution of 90gr of 48% HBr in acetic acid at 10 – 15°C. After stirring for 2hrs at room temperature reaction mixture was filtered and the solid washed with 100ml of IPA to get white crystalline citalopram hydrobromide of the formula I(a) (110gr). Purity by HPLC is 99.8%.

(b) Using ethyl acetate as solvent and HBr in acetic acid as HBr source.

To a stirred solution of citalopram (100gr) in ethyl acetate (500ml at 10 – 15°C was added commercially available 48% HBr in acetic acid (90gr) to get the pH 3.0 – 3.5. the resultant suspension was stirred for 2hrs at 25°C and filtered. The wet cake was washed with 50ml of IPA to get pure crystalline citalopram hydrobromide of the formula I(a) (100gr). Purity by HPLc is 99.8%.

(c) Using water as solvent and aqueous HBr as HBr source.

To a stirred suspension of pure citalopram base (100gr) in 300ml of water was added a solution of 90gr of 48% aqueous HBr at 10 – 15°C. After stirring for 8hrs at room temperature reaction mixture was cooled to 0 – 5°C and filtered. The solid was washed with 100ml of IPA to get white crystalline citalopram hydrobromide of the formula I(a) (110gr). Purity by HPLC is 99.8%.

Example – 5.

Recrystallization of citalopram hydrobromide.

(a) From methanol - IPA.

To 100gr of pure citalopram hydrobromide salt obtained as in example 4 above was added 200ml of methanol and heated to reflux temperature. After obtaining a clear solution, 200ml of IPA was added and cooled to room temperature. The reaction mixture was further cooled to 0 – 5°C and filtered off to get colourless crystals of citalopram hydrobromide of the formula I (a). Yield 98gr.

(b) From water.

To 100gr of pure citalopram hydrobromide salt obtained as in example 4 above was added 300ml of water and heated to 50 — 60°C. After getting a clear solution 5gr of carbon was added and filtered the solution. The filtrate was cooled to 10 – 15°C and maintained for 2hrs. the solid formed was filtered and the cake washed with 50ml of IPA to get the purified citalopram hydrobromide (95gr). HPLC:99.9%.

ADVANTAGES OF THE INVENTION

(i) Replacing hazardous lithium aluminium hydride with sodium borohydride for the preparation of unisolable magnesium salt of benzophenone derivative is very much cost effective

(ii) Avoidance of high vacuum distillation at the stage of formation of crude intermediate of the formula V into Formula VI makes the proves economical

(iii) Removing the impurities from the intermediate of the formula VI instead of from the compound of the formula V employing simple crystallization technique, thereby making the purification process simpler and more effective

(iv) improving the quality of citalopram formed in the reaction to an appropriate level making the quality of hydrobromide salt of pharmaceutical grade

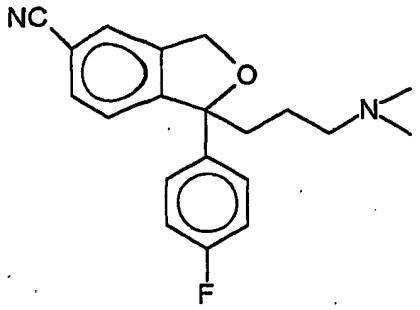
(v) selection of proper solvent system and conditions to keep the impurities present in citalopram in solution form while making the salt

(vi) selecting proper source of hydrogen bromide other than HBr gas to make the salt easier and of high purity and

(vii) avoiding recrystallization technique, if possible to minimize the losses of citalopram salt, especially hydrobromide salt thereby increasing the yield

We claim:

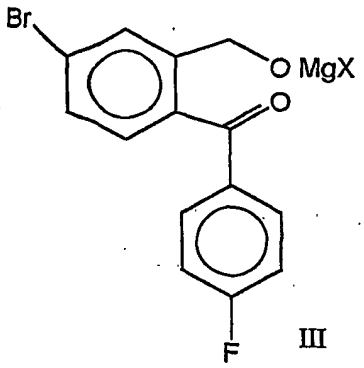
1. An improved process for the preparation of citalopram of the formula I.



I

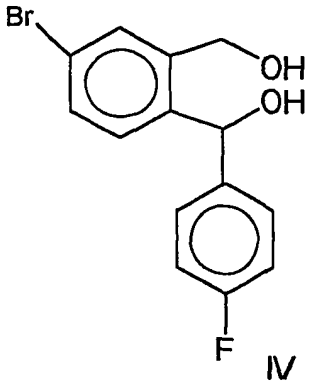
which comprises:

(i) preparing the compound of the formula IV by reducing an unisolaable magnesium salt of benzophenone derivative of the formula III .



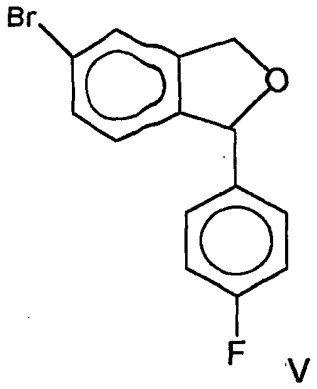
III

using sodium borohydride in the presence of a protic solvent



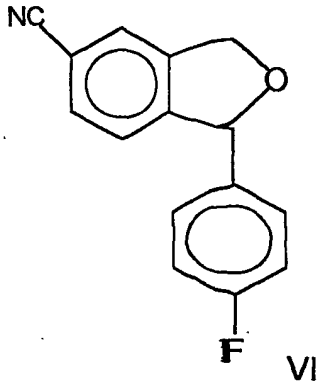
IV

(ii) reacting the compound of the formula IV obtained in step(i) with an acid catalyst in a non-polar solvent to obtain a compound of the formula V



V

(iii) reacting the compound of the formula V obtained in step (ii) with copper (I) cyanide in a polar solvent medium and isolating the resulting cyano compound, by re-crystallization by using polar and /or alcoholic solvents to obtain a reaction mass containing a compound of the formula VI



VI

(iv) reacting the compound of the formula VI with a strong base in DMSO medium followed by quenching with the required side chain to get the citalopram of the formula I.

(v) pouring the reaction mass obtained in steep (iv) above into water and extracting the citalopram into an organic solvent.

(vi) extracting the citalopram from organic solvent using dilute aqueous organic acid.

(vii) adjusting the pH of the resulting aqueous organic acid layer to 7.0 to 8.0 using a weak organic base.

(viii) extracting the liberated citalopram using a non-polar ether or aromatic solvent.

(ix) crystallizing the citalopram from the same solvent after concentrating and isolating by filtration and if desired.

(x) forming the pharmaceutically acceptable salt of the citalopram by conventional methods.

2. An improved process as claimed in claim 1 wherein the extraction of crude citalopram from the reaction mixture after water work up in step (v) is effected using non-polar aromatic solvents such as benzene, toluene, xylene or dialkyl ethers such as ethyl ether, isopropyl ether, methyl isobutyl ether, methyl t-butyl ether.

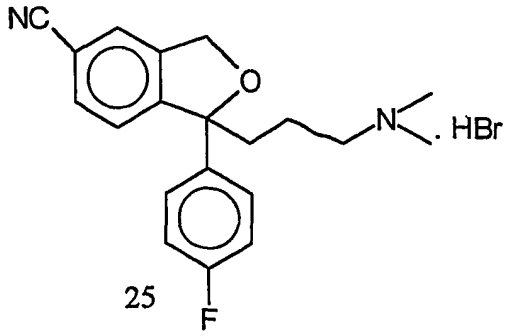
3. An improved process as claimed in claims 1 and 2 wherein the extraction of organic layer containing crude citalopram base obtained in step (vi) is done using aqueous organic acids such as acetic acid, propionic acid, succinic acid, oxalic acid.

4. An improved process as claimed in claims 1 to 3 wherein the neutralization of the aqueous organic acid layer containing citalopram base in step (vii) is effected using aqueous organic base such as ammonia, methylamine, diethylamine, triethylamine to a pH in the range of 7 to 8.

5. An improved process as claimed in claims 1 to 4 wherein the concentration of organic layer containing pure citalopram base in step (ix) is effected by distillation under vacuum at a temperature in the range of 40 — 60°C.

6. An improved process as claimed in claims 1 to 5 wherein the isolation of pure crystalline citalopram base from the organic solvent in step (ix) is effected by filtration at a temperature in the range of 0 – 25°C, preferably in the range of 20 – 25°C.

7. An improved process for the preparation of high purity (99.8%) citalopram hydrobromide salt of formula I(a)



I(a)

which comprises:

a. dissolution of high purity (99.5%) citalopram obtained by the process as claimed in claims 1 to 6 in a non- polar aromatic or dialkyl ether solvent and addition of molar quantity of 40 – 50% HBr in an organic acid.

b. isolating citalopram hydrobromide by filtration from the organic solvent of step (a) at a temperature in the range of 0 – 25°C, preferably in the range of 0 – 5°C and if desired.

c. recrystallization of citalopram hydrobromide obtained in step (b) from a mixture of alcoholic solvents.

d. suspension of the high purity (>99.5%) citalopram in water and addition of molar quantity of commercially available aqueous hydrobromic acid.

e. decolorization of the resulting solution with charcoal and crystallization of the citalopram hydrobromide.

f. Isolation of citalopram hydrobromide by filtration.

8. An improved process as claimed in claim 7 wherein the aromatic solvents used in step (a) is selected from benzene, toluene, xylene, preferably toluene.

9. An improved process as claimed in claims 7 & 8 wherein the dialkylethers used in step (a) is selected from diethyl ether, diisopropyl ether, methyl isobutyl ether, methyl t-butyl ether, preferably diethyl ether or diisopropyl ether and the like.

10 An improved process as claimed in claim 7 to 9 wherein the organic acid used in step (a) is selected from acetic acid, propionic acid, oxalic acid, succinic acid, prferably acetic acid or oxalic acid and the like.

11. An improved process as claimed in claims 7 to 10 wherein the extraction in step(c) is effected at a pH in the range of 7.0 – 8.0.

12. An improved process as claimed in claims 7 to 11 wherein the organic solvent used for extraction in step (b) is selected from solvents such as diethyl ether, isoporpyl ether, t-butyl methyl ether and the aromatic solvent may be selected from, toluene, benzene etc. preferably isopropyl ether or toluene.

13. An improved process as claimed in claims 7 to 12 wherein the ratio of organic solvent to base used in step (b) is in the range of 3-5 : 1, preferably 3:1.

14. An improved process as claimed in claims 7 to 13 wherein the temperature used in step (b) is in the range of 0 – 5°C.

15. An improved process as claimed in claims 7 to 14 wherein the mixture of alcoholic solvents used in recrystallization of high purity citalopram hydrobromide in step (c) is selected from ethanol, isopropanol, preferably methanol and isopropanol.

16. An improved process as claimed in claims 7 to 15 wherein the ratio of solvents used in recrystallization of high purity citalopram hydrobromide is selected from 1-3 : 2-6, preferably 1-2 : 2-4.

17. An improved process for the preparation of high purity (99.8%) citalopram of formula I substantially as herein described with reference to the Examples 1 & 2.

18. An improved process for the preparation of high purity (99.8%) citalopram hydrobromide salt of formula I(a) substantially as herein described with reference to the Examples 3 & 4.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IN 02/00167

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D307/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 066453 A (PULLA REDDY MUDDASANI ;VENKAIAH CHOWDARY NANNAPANENI (IN); NATCO P) 29 August 2002 (2002-08-29) page 8 -page 14; examples	1-18
Y	WO 98 19511 A (BECH SOMMER MICHAEL ;PETERSEN HANS (DK); BOEGESOE KLAUS PETER (DK)) 14 May 1998 (1998-05-14) claims	1-18
Y	US 4 136 193 A (TOFT ANDERS S ET AL) 23 January 1979 (1979-01-23) cited in the application column 2 -column 3; examples	1-18
Y	EP 0 171 943 A (LUNDBECK & CO AS H) 19 February 1986 (1986-02-19) page 3 -page 4	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2003	10/04/2003

Name and mailing address of the ISA	Authorized officer
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